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PATENT  
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Kathy Meuse

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thomas L. Benjamin et al. Art Unit: 1632  
Serial No.: 09/812,633 Examiner: Q. Janice Li  
Filed: March 19, 2001 Customer No.: 21559  
Title: DIAGNOSING AND TREATING CANCER CELLS USING SAL2

Commissioner for Patents  
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. THOMAS BENJAMIN, PhD

I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application.
  2. I have read the Office Action mailed on August 14, 2002 in connection with the above-referenced patent application.
3. We have found multiple polymorphisms in the Sal2 gene using techniques known in the art at the time the application was filed. For example, we have described


in the specification a polymorphism (on pages 36 and 37) at amino acid position 73 of the p150<sup>Sal2</sup> protein, characterized by the substitution of a serine residue with a proline residue. Referring to Figure 11, we have found loss of heterozygosity (LOH) at this site, or loss of the 73S allele, in an ovarian tumor relative to healthy tissue. Page 36 (line 28) of the specification also discloses of a G744R substitution in ovarian carcinoma cell lines, which we have also found in human ovarian tumor samples. In addition to the S73C and the G744R polymorphisms in the p150<sup>Sal2</sup> gene described throughout the specification (e.g., at pages 36 and 37), multiple polymorphisms associated with proliferative diseases have been found elsewhere in the p150<sup>Sal2</sup> gene (summarized in Exhibit 1). Tumor samples and matching healthy tissues isolated from heterozygous individuals were analyzed for LOH at such polymorphic positions. In particular, LOH at amino acid position 120 (S120P) was only observed in tumor samples (P/P) while healthy tissues were heterozygous (S/P). Based on our analysis of ovary tumor and normal tissue screened to date, we have found that LOH only occurs in tumor samples.

4. Exhibit 2 demonstrates that we have also found p150<sup>Sal2</sup> to be down regulated in a number of human tumors, in addition to ovarian cancer. Ubiquitin normalized cDNA arrays (Clontech), containing matched normal and tumor tissues from cancer patients, were hybridized with a p150 cDNA (*Sal2*) to analyze p150<sup>Sal2</sup> protein expression. Such arrays included the cDNA from 14 samples of kidney tumors and 11

samples of colon tumors. Out of fourteen kidney tumor samples, ten had a marked down regulation of p150<sup>Sal2</sup> gene product relative to normal control tissues (about 70% of tumors). Similarly, out of eleven of the colon tumor samples tested, eleven showed a down regulation of p150<sup>Sal2</sup> (100%). Based on this analysis, a down regulation of the protein is clearly associated with colon and kidney cancers. Techniques to detect protein levels were known in the art at the time of filing of the application and are provided, for example, in the specification on page 20 (lines 11-24).

5. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

2/14/03  
Date

  
Dr. Thomas Benjamin

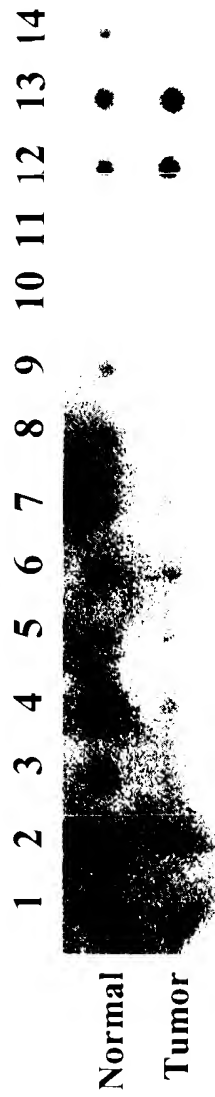
# EXHIBIT 1

Summary of mutations or polymorphism found in p150<sup>sal2</sup> gene in ovarian tumors.

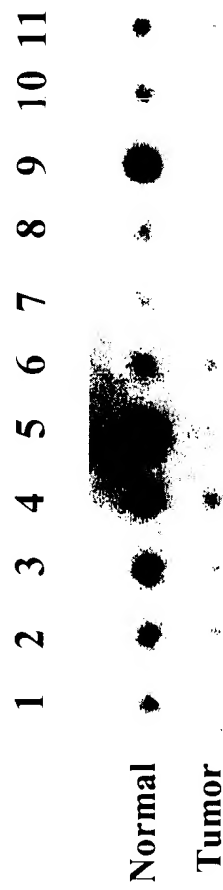
AA number	Dominant allele	Mutated or polymorphic allele
73	Serine (S)	Cysteine (C) * heterozygous S/C Found in both tumor and normal tissues normal tissue
120	Serine (S)	Proline (P) ** heterozygous S P and homozygous P P found only in tumor tissues
166	Proline (P)	Leucine (L) * heterozygous P/L Found in both tumor and normal tissues normal tissue
280	Glycine (G)	Alanine (A) * heterozygous G/A Found in both tumor and normal tissues normal tissue
515	Valine (V)	Glycine (G) * heterozygous V/G Found in both tumor and normal tissues normal tissue
744	Glycine (G)	Arginine (R) * heterozygous G/R Found in both tumor and normal tissues normal tissue
951	Alanine (A)	Glycine (G) * heterozygous A/G Found in both tumor and normal tissues normal tissue

# EXHIBIT 2

## Kidney Tumors



## Colon Tumors





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 Boulevard, Grand Central  
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Paul Taylor

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World's Health Champion  
World's Health Champion

Atkinson, D. and Curran, J. 2000. *Journal of the Philosophy of Education Society of Great Britain*, 30, 1, 1-16.

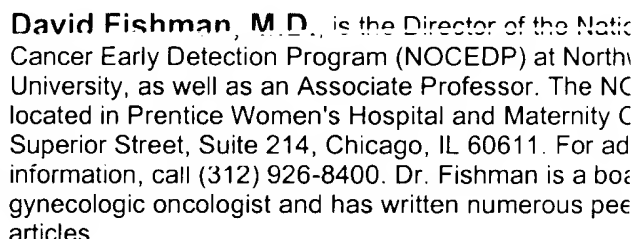
### References

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The American Cancer Society estimates that approximately 24,000 women are diagnosed with ovarian cancer each year. Ovarian cancer is the 5<sup>th</sup> leading cause of cancer death among U.S. women and has the highest mortality rate of all gynecologic cancers. The majority of women with ovarian cancer are diagnosed after the disease has reached an advanced stage (stage III or IV) because the symptoms of ovarian cancer are vague or “silent”. Despite advances in aggressive surgical intervention and new chemotherapeutic regimens, the 5-year survival rate for women with advanced stage ovarian cancer has remained constant, over the past 30 years, at approximately 15%. For those women diagnosed with cancer confined to the ovary (stage I), the overall 5-year survival is approaching 90%. Clearly, the need for early detection of ovarian cancer is the best way to improve survival. The National Ovarian Early Detection Program aims to do this.

The National Ovarian Cancer Early Detection Program, under the direction of David A. Fishman, is a collaborative effort between the National Cancer Institute, Northwestern University and the Robert H. Lurie Comprehensive Cancer Center of Northwestern. This collaborative effort integrates the biochemical and clinical studies of ovarian metastasis with the development of new serum and plasma markers for the early detection of ovarian cancer.

The purpose of the National Ovarian Cancer Early Detection Program (NOCEDP) is to identify those women who are at increased risk for ovarian cancer and to develop new tests, unique to the ovaries, to help detect ovarian cancer at an early, treatable stage. The requirements to enroll in the NOCEDP are:

program include one or more of the following: a personal history of breast or urinary cancer; one or more first degree relatives (mother, sister, with ovarian cancer; multiple family members with either breast and cancer; a personal history of a positive BRCA1 or BRCA2 genetic test; a close relative with a positive BRCA1 or BRCA2 genetic test result; a fertility drugs for more than one year.

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**Created:** 11/30/2000 - *David Fishman, M.D.*

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